IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#11
5/14/02
w/attachment

Applicants:	Groman et al.	Atty Docket:	1275/190
Serial No.:	09/521,264	Art Unit:	1619
Date Filed:	March 9, 2000	Examiner:	Wells, L.

Invention: Heat Stable Colloidal Iron Oxides Coated with Reduced Carbohydrates and Carbohydrate Derivatives

Commissioner for Patents
Washington, DC 20231

DECLARATION OF JEROME M. LEWIS, Ph.D. IN SUPPORT OF APPLICANTS' RESPONSE
[37 C.F.R. § 1.132]

Dear Sir:

In support of the accompanying response to the Office Action mailed November 2, 2001, in the above-reference matter, I hereby declare as follows:

1. My name is Jerome M. Lewis, Ph.D. I am Vice President of Scientific Operations, of Advanced Magnetics, Inc., the assignee herein, and one of the inventors of the subject matter of the above patent application. I am an inventor or co-inventor of a substantial number of patents involving (among other things) polysaccharide superparamagnetic iron oxide complexes and related materials and methods. I am also familiar with and have supervisory responsibility at Advanced Magnetics, Inc. in carrying out Current Good Manufacturing Practices (cGMPs) as required by the Food and Drug Administration. My further credentials are set forth in my Curriculum Vitae, which is attached hereto as Exhibit A.

2. I have read the action of November 2, 2001. This declaration is provided to clarify the record concerning polysaccharide superparamagnetic iron oxide complexes, and in particular the relations among edematous response, sterilization methods, and stability associated with such materials. This declaration is also provided to address the meaning of certain terms used in the above patent application.

Consideration of the Prior Art

3. There is no question that it would be highly desirable, from both regulatory and commercial perspectives, to have a polysaccharide superparamagnetic iron oxide complex as a pharmaceutical that when terminally sterilized (autoclaved) does not form particulates and that has minimal edematous response. I show below that, until the present invention, no such material existed.

4. First of all, the United States Food and Drug Administration (FDA) and its European counterpart have a policy that strongly favors terminal sterilization (autoclaving) over filter sterilization. The reason for this policy is that terminal sterilization provides a much higher level of sterility assurance than does filter sterilization. See presentation "Risk-Based CMC Microbiology Review" of David Hussong, Ph.D. of the FDA, copy attached as Exhibit B; European Commission (Directorate General III—Industry Pharmaceuticals and cosmetics), Vol. 4, *Good Manufacturing Practices—Medicinal products for human and veterinary use* (1998 Edition)(rules governing medicinal products in the European Union), p. 16 ("terminal sterilization in the final container is to be preferred"; "refraining from terminal sterilization in the final container should be justified in the application file")(copy attached as Exhibit C); *European Pharmacopoeia* (3d ed. 1997), p. 283 ("wherever

possible, a process in which the product is sterilized in its final container (terminal sterilization) is chosen"; "if terminal sterilization is not possible, filtration through a bacteria-retentative filter or aseptic processing is used")(copy attached as Exhibit D).

5. Second, polysaccharide superparamagnetic iron oxide complexes are opaque, and their nature prevents ordinary visual inspection by the end user (the physician) for the presence of microbial contamination. This factor makes it even more important to provide an extremely high level of assurance of sterility (which cannot be provided by filter sterilization) , and thus makes terminal sterilization even more important.

6. Nevertheless, terminal sterilization of polysaccharide superparamagnetic iron oxide complexes creates serious problems. These problems show up in the history of the development of such materials. Advanced Magnetics, Inc., where I have worked as a scientist for more than 15 years, has pioneered this development, as shown in the patents awarded to Advanced Magnetics in this field.

7. An early commercial material developed by Advanced Magnetics is now sold as Feridex®, and aspects of this material are disclosed (among other places) in U.S. patent 4,827,945 (this is the Groman patent cited by the Examiner), for both of which I am a co-inventor and both of which are assigned to Advanced Magnetics, Inc., the assignee of the present application. Feridex is the first commercial material of its type, approved by the FDA, and it is terminally sterilized. However, to permit the material to be terminally sterilized, citrate must be added. U.S. patent 4,827,945, col. 9, lines 26-32; col. 29, lines 15-36. Even with the addition of citrate, the material has an associated risk of particulate formation, which must be addressed in administration of the material. In particular, the material must be filtered at the time it is administered to the patient to assure removal of

these particulates. Another risk associated with the material is that of adverse reactions, measured in laboratory animal experiments as edematous response. Owing to the risk of adverse reactions, the material is administered only after dilution and is also administered slowly. Attached as Exhibit E is an FDA-approved package insert for this material which describes the dilution and use of the filter as well as risks of adverse reactions. (See "Dosage and Administration" near the end of Exhibit E.

8. The second generation of commercial material developed by Advanced Magnetics, called Combidex®, is a complex of ultrasmall particles. (This material has received an approvable letter from the FDA.) These particles have a different biodistribution due to their smaller size. Aspects of this material are disclosed (among other places) in U.S. patents 5,160,726 and 5,055,288 (this is the Josephson patent cited by the Examiner). Despite the facts that this is a second generation material and that regulatory policies favor terminal sterilization, this material is sterilized by filtration, not by terminal sterilization, in order to have satisfactory stability. See, for example, abstract and passim of U.S. patent 5,160,726. Furthermore, the use of filter sterilization here does not obviate the associated risk of particulate formation, which, as in the case of Feridex, must be addressed in administration of the material. In particular, the material must be filtered at the time it is administered to the patient. Another risk associated with the material, as in the case of Feridex, is that of adverse reaction, measured in laboratory animal experiments as edematous response. Owing to the risk of adverse reactions, the material is administered only after dilution and is also administered slowly.

9. The present application is directed to the third generation of material developed by Advanced Magnetics, and this material is presently in clinical trials. This material, like

Combidex, is a complex of ultrasmall particles and has a similar favorable biodistribution. This material is terminally sterilized, and unlike Feridex and Combidex, has a sufficiently small risk of particulate formation such that no filtration is required during administration.

10. Additionally, the risk of adverse reaction (measured in laboratory animal experiments as edematous response) associated with the material is significantly lower than in the case of Feridex and Combidex. This lower risk means that (unlike Feridex and Combidex) the material can be administered more rapidly and without dilution. The analysis set forth above for Feridex, Combidex, and the new material is summarized in the following table:

Material	**Sterilization method**	**Does particulate formation risk require filtration during administration?**	**Does adverse reaction risk require dilution and slow administration?**	**Edematous response?**
Feridex (Lewis, 5,055,288; Groman, 4,827,945)	Autoclaving following citrate addition	Yes	Yes	Yes
Combidex (Josephson, 5,160,726)	Filtration	Yes	Yes	Yes
New material (in present application)	Autoclaving	No	No	No

11. Consistent with the summary above etc. we note that other commercial contrast agents such as gadolinium based MRI contrast agents and iodine based CT contrast

agents are all sterilized by autoclaving and are administered without a filter or dilution all in compliance with the preferred regulatory requirements. Furthermore we note that not having to use a filter and being able to deliver these contrast agents without dilution serve commercial and medical needs also. Similarly, these properties are commercially and medically desirable in a iron based colloidal MRI contrast agent such as our third generation agent.

12. The materials of Maruno are inconsistent with the desirable regulatory, commercial and medical properties of a contrast agent. There is no teaching in Maruno of how to make stable materials that survive autoclaving. Nor is there any teaching in Maruno of materials that have decreased adverse reactions (measured in laboratory animal experiments as edematous response).

13. The materials of Maruno are filter sterilized. See, for example, patent 5,204,457, col. 15, lines 30-50 (Example 1 and Table 2); col. 16, lines 1-10 (Reference Example 4 and Table 3 use Example 1 procedures); and *passim*. See also, for example, patent 6,165,378, col. 17, lines 12-14 and 38-43; and col. 18, lines 9-13 and lines 48-50. Given the well-established and clear preference for terminal sterilization (autoclaving) discussed above, the only reason for using filter sterilization instead of terminal sterilization is the instability of the material as resulting from exposure to the relatively high temperature required for autoclaving. The only discussion in Maruno about autoclaving is in col, 11 of '457 around line 31, and, while the meaning of the passage, taken by itself, is not free from doubt, the "similar tendency" experienced in autoclaving his material seems to be precipitation or gelation, discussed in the previous sentence in the reference. Moreover, in context, we find that the Maruno references provide no detail of testing of the materials

for stability at temperatures above 80 degrees C. The absence of testing data above 80 degrees C, in combination with the use of filter sterilization, confirms, to a person of ordinary skill in the art, that the materials are indeed subject to precipitation or gelation at higher temperatures. In fact, most of the examples in Maruno '457—all but 3 and 7—even at 80 degrees suffer the same fate. And Maruno '378, despite the fact of having been filed 7 years later, contains no testing data whatsoever for stability at elevated temperatures. In short, the Maruno references teach that the materials disclosed therein suffer instability when subjected to temperatures above 80 degrees C.

14. In contrast, autoclaving normally requires temperatures of at least 121 degrees (see, for example, Exhibit C), and in any event at least 115 degrees C.

15. In conclusion, it is clear that the Feridex material of the prior art (Lewis and Groman references)—which I co-invented and which was developed at Advanced Magnetics, Inc., the assignee herein—is autoclaved only in the presence of citrate, has a risk of particulate formation requiring administration through a filter, and an adverse reaction risk requiring dilution and slow. The Combidex material of the Josephson reference, developed at Advanced Magnetics, Inc., the assignee herein, is filter sterilized, and, like Feridex, has a risk of particulate formation requiring administration through a filter, and an adverse reaction risk requiring dilution and slow administration. The Maruno references fail to teach anything about creating a material that can be autoclaved without degradation, and fail to teach anything about creating a material with decreased risk of adverse reactions. Finally, the new material (the subject of the present application) is stable to autoclaving, does not require dilution for administration, does not require

filtration during administration, and does not produce an edematous response in laboratory test animals.

Consideration of Certain Terms in the Patent Application

16. As to the meaning of certain terms in the patent application, the term "derivatizing" and related terms (e.g. derivatives, derivatized, derivatization, etc) is used in the application in the conventional sense well understood to a person of ordinary skill in the art. As one skilled in the art is aware, functionalization to produce derivatives occurs at the most reactive site on a molecule, the site termed the functional group. It is not necessary to state explicitly that this will be the site of derivatization, because a person skilled in the art already knows this. For example, *Solomon's Organic Chemistry, Sixth Edition*, John Wiley & Sons, Inc., New York, (1996)(excerpts attached as Exhibit F) p. 65 states "A functional group is the part of the molecule where most of its chemical reactions occur. It is the part that effectively determines the compound's chemical properties (and many of its physical properties as well). The functional group of an alkene, for example, is its carbon-carbon double bond." The functional group of an alcohol is the hydroxyl group, as defined in *Solomon's Organic Chemistry*, "Methyl alcohol .... is the simplest member of a family of organic compounds known as **alcohols**. The characteristic functional group of this family is the hydroxyl (OH) group ...." (id. p. 67). In the present invention, the reduced polysaccharide is a poly alcohol compound; thus, it contains multiple OH groups. All the OH groups are functional groups and thus potential reactive sites to form derivatives of the original compound.

17. In spite of the multiple OH groups, the possibilities for reactions and resulting derivatives with such a compound are limited, because as one skilled in the art would

understand, there are a limited number of reactions that occur with alcohols. As summarized in *Organic Chemistry, Second Edition* by K. P. C. Vollhardt and N.E. Shore, W. H. Freeman and Co., New York (1994) (excerpt attached as Exhibit G), pp. 278 there are basically four types of reactions that occur with alcohols: 1) reactions in base; 2) reactions in acid; 3) elimination reactions; and 4) oxidation reactions. Examples of compounds that can be formed as derivatives of alcohols include ethers, esters, acids, amides, and haloalkanes (via acid/base chemistry), aldehydes, ketones and acids (via oxidation reactions), and alkenes (via elimination reactions). Those are essentially all the derivatives one skilled in the art would envision for an alcohol. Therefore, the number and types of derivatives that can form from alcohols is finite, and consequently, using such terms as derivative or derivatizing within the context of this application is not vague and indefinite to one skilled in the art of basic organic chemistry.

18. In fact, prior art references of record in this proceeding use the same terminology. See, for example, Maruno 2 (United States patent 6,165,378). In the abstract, this prior art reference states: "The present invention provides a polysaccharide-magnetic metal oxide complex consisting of a polysaccharide derivative obtained by …." The term derivative is referred to throughout the document and is never defined per se. The term even shows up in the claims. For example, Claim 1 states: "A complex of a magnetic metal oxide and a polysaccharide derivative, wherein the derivative is obtained by carboxyalkyl-etherifying and aminoalkyl-etherifying a polysaccharide, where the aminoalkyl is optionally-substituted." See col. 19.

19. The term "ultrasmall" used in the present patent application is also well understood in the art. . For example, the Lewis patent (namely, patent 5,055,288, the

Lewis patent of record, cited by the Examiner as prior art and issued to Advanced Magnetics for my prior work with my colleagues in this area) is incorporated by reference in the present application, and the Lewis Patent discloses a reference by R. Weissleder entitled "Ultrasmall Superparamagnetic Iron Oxide: Characterization of a New Class of Contrast Agents for MR Imaging," *Radiology*, 75:489-493 (1990) (see U.S. Patent No. 5,055,288, p.2, Other Publications). The original Weissleder paper (copy attached as Exhibit H) describes a new class of contrast agents "small enough to migrate across the capillary wall, a prerequisite in the design of targetable particulate pharmaceuticals." See Abstract. Since this 1990 Weissleder publication, this new class of contrast agents, and the name for the class, abbreviated USPIOs, is cited throughout the contrast agent literature. For example, a quick search in the journal *Radiology* alone yielded five abstracts using the term "ultrasmall superparamagnetic iron oxide," from 1998 to the present. These abstracts are attached as Exhibit I.

20. I hereby declare that all statements made herein are of my own knowledge and that all statements made on information and belief are true; and further that these statements are being made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Jerome M. Lewis

Jerome M. Lewis, Ph.D.

Dated: April 25, 2002

Exhibits:

A - Curriculum Vitae of Jerome M Lewis, Ph.D.

B - Presentation "Risk-Based CMC Microbiology Review" of David Hussong, Ph.D. of the FDA

C - European Commission, Vol. 4, *Good Manufacturing Practices—Medicinal products for human and veterinary use* (1998 Edition), p. 16

D - *European Pharmacopoeia* (3d ed. 1997), p. 283

E - Feridex® package insert

F - Excerpts from *Solomon's Organic Chemistry, Sixth Edition* (1996)

G - Excerpt from *Organic Chemistry, Second Edition* (1994)

H - Weissleder, "Ultrasmall Superparamagnetic Iron Oxide: Characterization of a New Class of Contrast Agents for MR Imaging," *Radiology*, 75:489-493 (1990)

I - Abstracts from *Radiology* using the term "ultrasmall superparamagnetic iron oxide," from 1998 to the present

Exhibits:

A - Curriculum Vitae of Jerome M Lewis, Ph.D.

B - Presentation "Risk-Based CMC Microbiology Review" of David Hussong, Ph.D. of the FDA

C - European Commission, Vol. 4, *Good Manufacturing Practices—Medicinal products for human and veterinary use* (1998 Edition), p. 16

D - *European Pharmacopoeia* (3d ed. 1997), p. 283

E - Feridex® package insert

F - Excerpts from *Solomon's Organic Chemistry, Sixth Edition* (1996)

G - Excerpt from *Organic Chemistry, Second Edition* (1994)

H - Weissleder, "Ultrasmall Superparamagnetic Iron Oxide: Characterization of a New Class of Contrast Agents for MR Imaging," *Radiology*, 75:489-493 (1990)

I - Abstracts from *Radiology* using the term "ultrasmall superparamagnetic iron oxide," from 1998 to the present